ABSTRACT

The invention relates to a transdermal therapeutic system (TTS) for transcutaneously administering tolterodine over a period of several days and to a method for producing the same. The TTS contains a self-adhesive layer-shaped matrix composition which contains a (meth)acrylate copolymer comprising ammonium groups. The TTS also contains at least one plasticizer and up to 25 wt. % of tolterodine.

EXHIBIT A

THE USE OF DRUG/EXCIPIENT INTERACTION IN THE DESIGN OF CONTROLLED RELEAS DOSAGE FORMS

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ABSTRACT:

Physicochemical interaction of diclofenac sodium (Dna) with tow polymers of ammonio methacrylates coplymers (EuDragit RL and RS) was investigated. A strong ionic interaction was observed with EuDragit RL polymer while EuDragit RS polymer showed a weak interaction.

The stronger ionic interaction of EuDragit RL was related to its higher content of functional quaternary ammonium groups (10%) than EuDragit RS (5%).

In order to obtain an interaction complex in the solid powder form, four different methods were evaluated. These methods were, interaction from aqueous Drug solution using either polymer powder (adsorption complex) or polymer in a form of aqueous dispersion (aqueous dispersion adsorption complex), and film formation by coevaporate either from aqueous dispersion of polymer and Drug aqueous solution (aqueous dispersion film) or from methanolic solution of polymer and Drug (organic film). Different ratios of Drug and polymer were used and affect of curing and aging on the plysicochemical properties of the interaction complex were evaluated by varity of methods such as dissolution in different media, X-ray powder diffractometry, FTIR and proton nuclear magnatic resonance (NMR) spectroscopic techniques.

The pre;iminary experiments of adsorption showed that each 1g of EuDragit RL powder, interacted with 0.16 - 0.17g of DNa. This ratio did not change when aqueous dispersion of EuDragit RL having enormous surface area, was used, however the equilibrium rates was highlt enhanced. This suggested that this interaction was independant of surface area and lead to propose a mechanism of ionic interaction.

The X-ray powder diffration patterns of Drug polymer ratios 1:5 and 1:10 clearly suggested the presence of DNa in a noncrystalline state, while the ratio of 1:1 showed diffraction peaks of crystalline DNa . At high ratio of polymer were the Drug existed as an ionic interaction complex, the X-ray diffraction peaks of DNa disappeared.

FTIR spectra supported the proposal of ionic-interaction mechanism. The spectra of Drug : polymer complex of 1:5 and 1:10 ratios when compared with the corresponding physical mixters indicated an ionic interaction. There was a significant decrease in intensity of peaks corresponding to carboxylate ions of DNa and quaternary ammoniuo groups of the polymer at wavenumbers 1500-1700 cm^{-1} and 800-900 cm^{-1} respectively. No clear evidence was observed for the occurrence of hyDrogen bonding between DNa and EuDragit RL polymer.

The interaction between DNa and EuDragit Rl polymer was inhibited by an ionic surfactants (sodiuom lauryl sulphate SLS) while was not affected by nonionic surfactants (Tween 80). Also , the release of Drug from the complex was greatly enhanced by SLS and was not affected by Twean 80. Thus, SLS exerted a displacement ionic reaction and supported the existence of ionic interaction mechanism between DNa and EuDragit RL polymer.

Drug release kinetics was found to be affected by factors such as Drug to polymer ratio, dissolution media, addition of surfactants, and pH. In general, higher polymer ratio brought the system closer to Fickain diffusion for example 1:10 possessed Fickian

diffusion over all the period of dissolution (24hr) while 1:5 ratio deviated after 15hrs. Dissolution in buffer medium caused the release mechanism to deviate from Fickian diffusion in first few hours of dissolution test. Addition of sodiuom lurly sulphate increased the rate of release significantly and usually Favoured Fickian diffusion. In distilled water, systems behaved closer to Fickian than in buffer solution.

Some systems possessed first order kintics indicating that mechanism of release was also dependant on matrix Drug load.

The possible use of SLS as release controlling agent was also investigated using organic film as well as matrix tablets made up of adsorption complex 1:5. As concentration of SLS increased the release rate and extent was increased. Incorporating SLS within matrix caused attrition-disintegration of tablet and resulted in a relatively higher initial release of Drug. However, presence of SLS both within matrix and disolution media caused the highest rate and extent of release.